IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kent C. COCHRUM *et al.* Group Art Unit: 1651

Application No.: 09/438,872 Examiner: MARX, I.

Filed: November 12, 1999 Attorney Docket No.: 44041.010400

For: HEMOSTATIC POLYMER USEFUL FOR RAPID BLOOD COAGULATION AND HEMOSTASIS

MAIL STOP APPEAL BRIEF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1, 3, 9, and 11-13. Claims 29-36, the only claims pending in this application have been withdrawn from consideration by the Examiner.

REAL PARTY IN INTEREST

This application is assigned to Polymer Biosciences, Inc.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

Claims 1, 3, 9, 11-13 and 29-36 were pending in this application when the final rejection was issued by they Examiner. Claims 1, 3, 9, and 11-13 were rejected and claims

29-36 were withdrawn from consideration. Appellant did not respond to the final rejection but rather filed this appeal. Hence, claims 1, 3, 9 and 11-13 are before the Board in this appeal. A copy of the claims on appeal is attached as appendix A hereto.

STATUS OF AMENDMENTS

No reply to the final rejection was submitted. A notice of appeal was filed in lieu thereof.

SUMMARY OF THE INVENTION

The present invention relates to a novel hemostatic polymer composition comprising a reaction product of a polymer containing uncharged organic hydroxyl groups and a substance containing at least one of a halogen atom and/or an epoxy group. This polymeric is composition useful for the rapid induction of blood coagulation and hemostasis at a wound or bleeding site. (Spec. p.1, l. 5-8).

The present hemostatic polymer composition significantly promotes healing of tissues in a cascade-like fashion without the use of exogenous thrombin.

The hemostatic polymer composition of the invention also reduces the risk of blood borne diseases (HIV and hepatitis) since the fibrinogen is concentrated from the patients own blood in vivo.

The novel hemostatic polymer composition eliminates or strongly reduces the risk of immunogenic reactions. (Spec. p. 11, l. 20-26).

Blood coagulation and hemostasis occur upon contact of the polymer composition with blood or bleeding tissue without addition of exogenous thrombin. Blood coagulation and hemostasis occur upon contact of the hemostatic polymer composition with arterial blood flow or venous blood flow. (Spec. p. 12, l. 3-6).

"Hemostatic polymer composition" also called "hemostatic polymer" means a solution

or other preparation which contains essentially two components: a substance containing uncharged organic hydroxyl groups and a substance containing at least one of a halogen atom and/or an epoxy group. The composition may also be referred to as HP 15. HP 15 means 1 gram of G-150 that swells 15 times its original volume when placed in an aqueous environment. Its molecular weight exclusion limit is 3×10^5 or greater. Likewise, HP 20 is a modified form of HP 15 with lesser degree of cross-linkage. As well, its molecular weight exclusion limit is 5×10^5 or greater.

"Cascade-like effect" means a sequence of reactions beginning with applying the hemostatic polymer of the invention to the wound or incision, where the hemostatic polymer rapidly triggers release of various clotting factors, and other ancillary substances, which initiate the physiological clotting process. Since the polymer is not a natural substrate for plasmin/plasminogen lytic reactions, the hemostatic reaction continues unabated until hemostasis is achieved. (Spec. p. 15, l. 1-14).

The present invention is based upon the discovery that the homeostatic polymer composition is able to induce rapid blood clotting by concentrating the patients fibrinogen *in vivo* at the site of the wound or bleeding site. The hemostatic polymer composition, acting in concert with the concentrated fibrinogen activates the patients platelets and RBC's to convert prothrombin to thrombin without the addition of exogenous thrombin. See Figure 11. It is understood that the use of the hemostatic polymer composition is not intended to be limited to the examples appearing here below. Indeed, the hemostatic polymer composition is useful for rapid blood coagulation in all mammals, including humans

Hemostasis is achieved in cascade-like fashion caused by rapid and continuous activation and aggregation of the endogenous platelets present in the patients plasma. Due to this cascade-like effect, the adhesing strength of the hemostatic polymer increases well beyond the time (3-5 minutes) during which the maximal adhesive strength is obtained

physiologically or with fibrin glues, and continues until the complete hemostasis occurs. (Spec. p. 15, 4th line from the bottom to p. 16, l. 9).

The composition of the invention are characterized as preventing or excluding certain molecular weight components from entering the beads, thereby effectively concentrating the excluded components outside or away from the surface of the beads,. This molecular weight exclusion limit, however, varies with the type of blood components that are absorb by the beads. (Spec. p. 22, l. 5-9).

ISSUES ON APPEAL

Are claims 1, 3, 9, 12 and 13 anticipated within the meaning of 35 U.S.C. §102(b) by Great Britain 1,454,055 (hereinafter GB '055)? Is claim 11 obvious within the meaning of 35 U.S.C. §103(a) over GB '055 in view of Larson or Eloy et al. and Wang?

GROUPING OF THE CLAIMS

Appellant concede that all of the pending claims stand or fall together.

ARGUMENT

The Examiner has alleged that claims 1, 3, 9, 12 and 13 are anticipated by GB '055 as follows:

"GB '055 discloses a would dressing comprising dextran-epichlorohydrin polymer particles or beads and a matrix which may be paper, cotton fabric, inert plastics, etcs. Disinfectants may be added tot eh carrier. Sterilization may be gamma irradiation.

With respect to the added limitation regarding the property of the cross-linked dextran of triggering release of "clotting factors and other ancillary substances", this function is an inherent property of cross-linked dextrans."

Additionally, the Examiner believes that claim 11 is obvious over GB '055 in combination with Larson or Eloy et al and Wany for the following reasons:

"The claim is directed to a dry, stable, sterile would dressing comprising a matrix containing a hemostatic polymer such as cross-linked dextran and collagen or thrombin or fibrinogen.

Collagen, fibrinogen or thrombin are known hemostatic agents as describe by Larson or Eloy et al.

Wang teaches that cross-linked dextran has hemostatic properties.

The addition of thrombin or fibrinogen or collagen to the wound dressing of GB '055 would have been obvious when the reference was taken with Larson or Eloy et al. and Wang because cross-linked dextran, thrombin, fibrinogen and collagen are known hemostatic agents and have been used in the past as such.

It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art."

A. CLAIMS 1, 3, 9, 12 AND 13 ARE NOT ANTICIPATED BY GB '055

A brief, non-limiting summary of the present invention is offered to assist the Board's understanding both of the features of the claimed invention and of how these features distinguish the claimed invention from the prior art. The present invention relates to a hemostatic agent or polymer composition comprising beads or grains of a crosslinked dextran which are useful for the rapid induction of blood coagulation and hemostasis at an active bleeding site. The grains or beads absorb low molecular weight (MW) blood and plasma constituents into the grains or beads, while high MW constituents such a fibrinogen, platelets,

and clotting factors are concentrated on the surface of the grains or beads. This concentration results in rapid blood coagulation and hemostasis without the use of extraneous or other exogenous compounds.

GB '055 fails to teach to suggest a hemostatic polymer composition comprising beads or grains of a crosslinked dextran which is useful for the rapid induction of blood coagulation and hemostasis at a bleeding site.

GB '055 discloses a preparation for treating or cleaning a fluid-discharging surface, wound, sore, or mucous membrane. While GB '055 and the present application are both dextran-epichlorohydrin polymers, the consistency of the polymer in GB '055 is such that high molecular weight (e.g., MW 50000-270000) degradation products of fibrinogen are partly or completely excluded from the gel particles of that polymer. Thus, the concentration of both fibrin monomers and crosslinked fibrin on the actual liquid-discharging surface of the wound can be controlled so that subsequent scar formation does not take place on that surface by at a distance therefrom. **Rapid blood coagulation and hemostasis at an active bleeding site is not an intended use of the invention claimed in GB '055.**

In contrast, the present invention relates to a hemostatic agent and polymer composition comprising beads or grains of a crosslinked dextran molecule. The crosslinked dextran concentrates fibrinogen of the surface of the beads which in turn triggers rapid blood clotting and hemostasis directly at the active bleeding site, where such materials remain.

The instant claims are limited in a way such that cross-linked dextran beads which do not induce clotting at a bleeding are excluded from the claims.

GB '055 relates to a method for treating fluid-discharging skin surfaces, wounds and mucous membranes. It is pointed out that in GB '055 blood coagulation which promotes scar formation is disadvantageous on a liquid-discharging skin surface. GB '055 asserts that the concentration of fibrin monomers and cross-linked fibrin immediately adjacent to the

discharging surface should be as low as possible. It is an objective of GB '055 to prevent scar formation, i.e. to prevent blood clotting at the liquid discharging surface. At p. 2, lines 85-90, GB '055 specifically states that coagulation does not take place on the discharging surface.

The cross-linked dextrans which can be used in the GB '055 method can be chosen from a wide range of cross-linked dextrans. However, the useful cross-linked dextrans should be such that

> "...fibrin and fibrin coagulation cannot be formed ... in the zone adjacent to the discharging surface."
>
> (See p. 3, lines 96-106).

It is readily apparent from the entire GB '055 disclosure that rapid blood coagulation and hemostasis at an active bleeding site is not contemplated by this patent. Furthermore, the cross-linked dextrans which are useful in the GB '055 invention must be such that blood coagulation and hemostasis does not occur at a wound or bleeding site.

In contrast, the present invention relates to a hemostatic agent and polymer composition comprising beads wherein the cross-linked dextran beads concentrate fibrinogen on the surface of the beads which in turn triggers rapid blood clotting and hemostasis directly at the active bleeding site.

To constitute an anticipation, all the claimed elements must be found in exactly the same situation and united in the same way to perform the identical function in a single unit of the prior art. *Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 f.2d 724, 726, 220 U.S.P.Q. 841, 842 (Fed. Cir. 1984); *Integra LifeSciences I Ltd. v. Merck KgaA*, 1999 WL 398180, *398180, 50 U.S.P.Q.2d 1846, 1848 (S.D.Cal. 1999).

The invention in GB '055 uses cross-linked dextran such that substances are excluded from the dextran epichlorohydrin polymer particles migrate towards the outer layer of the particle mass, and blood coagulation at the wound surface is prevented. There is no

disclosure in GB'055 directed towards application of the covering to an active bleeding site.

The cross-linked dextran composition of the present invention as defined in claim 1 fixes fibrinogen and other clotting factors on the surface of the polymer beads or grains to form a biodegradable clotting matrix which remains in the active bleeding site. This type of material is clearly excluded from being useful in the invention of GB '055.

GB '055 fails to teach or suggest any hemostatic composition comprising beads of a cross-linked dextran which can provide for the rapid induction of blood coagulation and hemostasis at a bleeding site. The instant claims clearly define the use of cross-linked dextrans which promote clotting at a wound surface. Such is not the case with GB '055 which uses dextrans which do not cause such an effect. It is urged that the present claims define an invention which is patentably distinct from the invention of GB '055. Appellant respectfully submits that the present invention is not anticipated by GB '055.

Instant claim 1 specifies the molecular weight exclusion of the cross-linked dextran and that the nature of the beads is such that the beads induce a physiological clotting process at a bleeding site. The instant claims are limited in a way such that cross-linked dextran beads which do not induce clotting at a bleeding are excluded from the claims. The Sephadex that is the basis of GB '055 is Sephadex G-25 (MW Exclusion limit; 5,000 and water regain 2.5 ml/gm. Sephadex G-50 (MW Exclusion limit: 30,000 and water regain 5.0 ml/gm) will act somewhat similar to the G-25 but the G-25 clearly makes a clot that is well adhered to the tissue at the site of bleeding.

The main issue with MW range of the cross-linked dextrans used in the present invention is that they all have a relatively high rate of water regain compared to the preferred embodiment of GB '055. The preferred embodiment of the invention would be the G-150 with a water regain of 15 ml/gm of dry polymer. The preferred embodiment of GB '055 is G-25 with a water regain of only 2.5 ml/gm of dry polymer. At the lower level of water regain

you do not form a clot like material in blood but more of a loosely associated gel. However, with the higher rate of water regain associated with G-150, you get a very will formed clot like material that is adherent to the underlying tissue. This is due to the concentrating effect on the active coagulation factors as described in the present patent application., This process does not take place in GB '055 because they state on page 3, line 96, that "The particles should normally absorb water and swell at a rate which is sufficiently high that fibrin and fibrin coagulum, cannot be formed by the influence of the enzyme thrombin etc. in the zone adjacent the discharging surface." The difference with the preferred embodiment in the present application is that just the opposite occurs sand that is the rate is sufficiently high enough to produce a rapid concentration of the clotting factors including fibrin and thrombin at the site of bleeding and this forming a durable clot like material which is adherent to the bleeding tissue.

A second factor besides water absorption is that the molecular weight range of polymers used in the invention all absorb the potent anticoagulant substance present in plasma because they have molecular cut of 100,000. Thus in a preferred embodiment of GB '055 with a molecular cut of 5000, these anticoagulant substance are concentrated on the outside of the polymer along with the coagulation factors and thus inhibit the formation of a clot like substance which is what is required if the resulting gel is to be easily washed off the tissue. The anticoagulant substance include the following:

1) Heparin (a sulphated glycosaminoglycan), plasma concentration of 30-800 ng/ml, MW 5000 to 30,000.

2) Heparin Cofactor II (HCII), plasma concentration of 0.5 to 1.4μg/ml, MW 58,000.

3) Antithrombin III (ATIII), plasma concentration of 125μg/ml, MW 58,000.

4) Tissue Factor Pathway Inhibitor (TFPI), plasma concentration of 100 ng/ml, MW 43,000.

5) C1 Esterase Inhibitor (C1INH), plasma concentration of 100 μg/ml, MW 104,000.

6) Protein C, plasma concentration of 4 μg/ml, MW 21,000.

7) Protein S, plasma concentration of 20 to 25 μg/ml, MW 69,000.

Low molecular weight cut off polymers such as G-25 would concentrate all of these substances along with the essential clotting factor and thus act to inhibit coagulation. Once the molecular weight cut off is high enough to allow these anticoagulant substance to enter the polymer, then their concentration would be rapidly reduced in the material on the surface of the polymer and partitioned away from the coagulation factors. Thus the combination of rapid removal of water and partitioning of lower molecular weight anticoagulant surface away from the high molecular weight clotting factors such as thrombin and fibrin creates the proper environment for the formation of a adherent clot at the site of active bleeding.

It is urged that GB '055 does not direct the artisan to the physical characteristics of the polymers that stop bleeding and adhere to the bleeding tissue to form a clot in comparison to the polymers that act as a would cleaning system, moving fluid and protein away from the site of exudation. GB '055 does not provide an enabling disclosure from which the artisan could have made or used the instant invention by requiring that clotting is not occurring at the surface of the wound.

For the above reasons, appellant urges that GB '055 fails as a proper anticipation of the present claims. The secondary reference relied upon by the Examiner fail to remedy the deficiencies of GB '055.

B. CLAIM 11 IS NOT OBVIOUS OVER THE COMBINATIONS OF REFERENCES CITED BY THE EXAMINER.

As for Larson or Eloy et al., assuming *arguendo* that these references teach what the Examiner alleges, these citations do not teach or suggest the use of cross-linked dextran beads

or grains as a hemostatic agent. This is the main disability and failing of GB '055 and the '366 Patent.

None of the secondary references relied upon by the Examiner remedy the serious defects of the GB '055 patent as set forth above.

C. THERE IS NO SUGGESTION TO COMBINE ANY OF THE REFERENCES.

Finally, there is no suggestion in any of the aforementioned references to combine their disclosures in a manner which discloses either the compositions or methods of use of the compositions claimed in the present invention. Appellant urges that any possible combination set forth by the Examiner would not comprise the elements of the claimed invention and would be improper because the references taken alone or together do not teach or suggest the present invention. Such a combination is proper only when there is some objective teaching in the prior art that would lead one of ordinary skill in the art to combine the relevant teachings of the references. *In re Fine*, 5 U.S.P.Q. 2d 1956, 1598 (Fed. Cir. 1988)

In summary, appellant urges that the Examiner's combined references do not make out a *prime facie* case of obviousness against appealed claim 11.

CONCLUSION

Appellant urges for the reasons given above that the present claims are allowable over the applied prior art. The Examiner is requested to reconsider the §102 and §103 rejections and withdraw these rejections.

If the Examiner maintains these rejections, appellant respectfully request that the Board reverse the Examiner's §102 and §103 rejections.

Respectfully submitted,

Dated: 01/06/04

By: _____

Eugene C. Rzucidlo
Registration No. 31,900
Customer Number: 32361

APPENDIX A

1. A dry, storable stable, sterile dressing for application to a bleeding site which comprises a dry hemostatic zone, said zone comprising a matrix containing hemostatis-promoting amount of a hemostatic agent which accelerates blood coagulation and clot formation at an interface between the bleeding site and the hemostatic zone wherein said hemostatic agent comprises beads of cross-linked dextran wherein said cross-linked dextran has a molecular weight exclusion limit of 100,000 to 650,000 and triggers release of clotting factors and other ancillary substances which initiate a physiological clotting process when applied to the bleeding site.

3. The dry, sterile, dressing according to claim 1 wherein the hemostatic zone is affixed to a substrate.

9. The dressing of claim 1, wherein the dextran is crosslinked with epichlorohydrin.

11. The dressing according to claim 1, wherein the hemostatic agent further contains at least one of collagen, fibrinogen and thrombin.

12. The dressing according to claim 1, wherein the matrix further comprises a pharmaceutical agent.

13. The dressing according to claim 12, wherein said pharmaceutical agent is at least one of anti-inflammatory analgesic agents, steroidal anti-inflammatory agents, antihistamines, local anesthetics, bactericides or disinfectants, vasconstrictors,

chermotherapeutic drugs, antibiotics, keratolytics, cauterizing agents, or antiviral drugs.